सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

IB03/05140

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.**1155/Del/02** dated 15th **November 2002.***

Witness my hand this 16th day of March 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

1195 DEL 02

FORM 1

15 NOV 2002

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED,** a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled " **BIGUANIDE-GLITAZONE COMBINATIONS FOR DIABETES** "

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. SUMIT MADAN

b. ANUPAM TREHAN

c. VINOD KUMAR ARORA

d. RAJIV MALIK

DUPLICATE

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India,

all Indian Nationals.

4. That we are the assignee or legal representative of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6342001 – 10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, SUMIT MADAN, ANUPAM TREHAN, VINOD KUMAR ARORA, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representative.

a. (SUMIT MADAN)

b. (ANUPAM TREHAN)

c. (VINOD KUMAR ARORA)

d. (RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

   a. Complete Specification (3 copies)

   b. Drawings (3 copies)

   c. Statement and Undertaking on FORM – 3

   d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **685385** dated **23.10.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this 5TH day of **November**, 2002.

For Ranbaxy Laboratories Limited

Vinay Kumar Kaul
Whole-time Director

(SUSHIL KUMAR PATAWARI)
Company Secretary

RANBAXY LABORATORIES LTD. N. Delhi

1165 DEL 02

15 NOV 2002

FORM 2

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

BIGUANIDE – GLITAZONE COMBINATIONS FOR DIABETES

DUPLICATE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a novel pharmaceutical composition for oral administration of combination of antidiabetic agents wherein one is present in an extended release form and the other in an immediate release form.

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, insulin resistance, and is often associated with other disorders such as obesity, hypertension, hyperlipidemia, as well as complications such as cardiovascular disease, retinopathy, neuropathy, and nephropathy. The disease is progressive in nature, and can often be controlled initially by diet alone, but generally requires treatment with drugs or injections of exogenous insulin.

Biguanides have been the most widely used class of antidiabetics, they act by increasing insulin activity in peripheral tissues, reducing hepatic glucose output due to inhibition of gluconeogenesis and reducing the absorption of glucose from the intestine. Metformin, phenformin, buformin, etc. belong to this group. Metformin has been widely prescribed for lowering blood glucose in patients with non-insulin-dependent diabetes (NIDDM), marketed in 500, 850 or 1000mg strengths. However, being a short acting drug, metformin requires twice-daily or three-times-a-day dosing (500 - 850 mg tab 2-3x/day or 1000 mg bid with meals). Adverse events associated with metformin use are anorexia, nausea, vomiting and diarrhea, etc. The adverse events may be partially avoided by either reducing the initial and / or maintenance dose using an extended-release dosage form. Another advantage of an extended-release dosage form is a reduction in the frequency of administration.

More recently, glitazones have been introduced and are widely used in the treatment of NIDDM. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue in several NIDDM animal models, resulting in the correction of elevated plasma levels of glucose, triglycerides and nonesterified fatty acids without the occurrence of hypoglycemia. These agents, also known generically as thiazolidinediones, such as troglitazone, rosiglitazone and pioglitazone, work by increasing the sensitivity of peripheral tissues, such as skeletal muscle, towards insulin. Pioglitazone, the most widely used glitazone, is normally administered at doses from about 15 mg to about 45 mg, given as a single dose once per day. Another glitazone, rosiglitazone is administered at doses of about 5 mg to about 10 mg per day.

US 6,011,049 discloses that combination therapy with a biguanide and a glitazone results in dramatic improvement in glycemic control, and a better control can be achieved by using this

combination. Similarly combination treatment with once-daily metformin-rosiglitazone has been proved to improve glycemic control, insulin sensitivity, and Beta-cell function more effectively than treatment with metformin alone.

Although extended-release formulation of biguanide alone, as well as biguanide (conventional) in combination with a glitazone are well known now, but no such formulation is available which can provide the combined benefits of biguanide once-daily and glitazone in a single dosage form for once-a-day administration. This combination administered in a single dosage form for once daily administration will not only improve patient compliance but also save time and cost for preparing two different dosage forms.

In the present invention we have found that a combination of a glitazone as immediate release form and a biguanide as extended release form, administered once daily provide equivalent efficacy when compared to an extended release biguanide and glitazone in separate dosage forms administered together.

Therefore, the present invention is related to a novel pharmaceutical composition for oral administration, comprising a combination of a biguanide and a glitazone, wherein the biguanide is present as extended release form and the glitazone is present as immediate release form in a single dosage form.

The invention provides a dosage form containing both glitazone and biguanide. The glitazone is contained in an immediate-release form, so that it is released substantially immediately upon ingestion (i.e. upon swallowing). Generally at least 80% of the glitazone is released from the dosage form within an hour after administration. The biguanide, by contrast, releases in a sustained fashion, at least about 75% of the drug contained in the dosage form releasing over a period of 4 to 36 hours, preferably about 8 to 24 hours. The term "about" as used above and elsewhere herein means plus or minus 10% for each of the numerical limits.

Biguanide as employed herein is intended to include metformin, phenformin, buformin and the like.

Glitazone as employed herein is intended to include pioglitazone, rosiglitazone, troglitazone, ciglitazone, englitazone and the like.

The pharmaceutical compositions of the present invention can be administered orally in the form of tablets such as coated tablets or bilayered tablets; or in form of capsules containing pellets, beads. granules, multiparticulates, tablets or powder.

A glitazone can be incorporated into the dosage form as an immediate release component in a variety of ways. For example, it can be incorporated into an exterior coating for a tablet from which it releases substantially immediately upon ingestion. Such a coating can similarly be applied to each of the particles comprising a multiparticulate, i.e. granules, beads. If the dosage form is to be a capsule, glitazone can be contained in a single pellet inside the capsule from which it releases substantially immediately once the capsule shell dissolves. Alternatively, the glitazone can be contained in several smaller pellets or be present as immediate release particles or as immediate release layer over the extended release cores or beads. The coating composition may comprise water-soluble polymers such as polyvinyl pyrrolidine, hydroxypropyl cellulose, polyvinyl alcohol, hydroxypropyl methylcellulose and the like. The polymer may be applied as a solution in an organic solvent or as an aqueous dispersion. The solvent may be selected from water; alcohols like ethyl alcohols or isopropyl alcohol; ketones like acetone, or ethylmethyl ketone; chlorinated hydrocarbons like dichloroethane and trichloroethane. The coating composition may also comprise plasticizers, opacifiers and colorants. Any conventional coating equipment may be employed to facilitate coating such as centrifugal fluidized bed coating apparatus, pan coating apparatus, or fluidized bed granulating coating apparatus.

Due to poor dispersibility in solvents, the coating composition comprising the glitazone may also include a wetting agent. Suitable wetting agents for use in conjunction with the present invention include hydrophilic and hydrophobic surfactants. Hydrophilic surfactants may be selected from the group consisting of hydrophilic non-ionic surfactants, hydrophilic ionic surfactants, and combinations thereof. Hydrophobic surfactant may be selected from the group consisting of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty acid monoesters; glycerol fatty acid diesters; acetylated glycerol fatty acid monoesters; acetylated glycerol fatty acid diesters, lower alcohol fatty acid esters; polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers, polyethyleneglycols as esters or ethers, polyethoxylated castor

oil; polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor oil or polyethoxylated fatty acid from castor oil or polyethoxylated fatty acid from hydrogenated castor oil.

The biguanide may be incorporated in an extended release core by dispersing in a rate controlling polymer matrix; or biguanide may be layered onto pharmaceutically acceptable inert cores or seeds, which is surrounded by rate controlling polymer layer.

The term matrix, as used herein, refers to a uniform mixture of a biguanide, rate-controlling polymers and optionally other excipients. The rate-controlling polymers may be hydrophilic, hydrophobic or a combination thereof. The rate-controlling polymers are uniformly dispersed throughout the matrix to achieve uniform drug release. Hydrophilic polymers of the present invention include cellulose derivatives such as hydroxypropylcellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose or combinations thereof. The hydrophobic polymers may be selected from poly (ethylene) oxide, ethyl cellulose, cellulose acetate, cellulose acetate butyrate, hydroxypropyl methylcellulose phthalate, poly (alkyl) methacrylate, and copolymers of acrylic or methacrylic acid esters, waxes, shellac and hydrogenated vegetable oils.

In addition to the active and rate-controlling polymers, the matrix of the present invention may contain other pharmaceutically acceptable excipients, which act in one or more capacities as diluents, binders, lubricants, glidants, colorants or flavoring agents. The matrix may be made by any pharmaceutically acceptable technique that achieves uniform blending, e.g. dry blending, wet granulation, compaction and fluid bed granulation.

Suitable diluents include pharmaceutically acceptable inert fillers such as microcrystalline cellulose, lactose, dibasic calcium phosphate, mannitol, starch, sorbitol, sucrose, dextrose, maltodextrin or mixtures thereof.

Suitable binders may be selected from polyvinyl pyrrolidone, lactose, starches, gums, waxes, gelatin, polymers or mixtures thereof.

Suitable lubricants include colloidal silicon dioxide, talc, stearic acid, magnesium stearate, magnesium silicate, polyethylene glycol, sodium benzoate, sodium lauryl sulphate, fumaric acid, zinc stearate, paraffin, or mixtures thereof.

Suitable glidants may be selected from talc and colloidal silicon dioxide.

The matrix formed can be compressed to form the tablets.

Beads or pellets can be prepared using techniques like extrusion-spheronization, drug layering, granulation and the like. The inert core or seeds may be water soluble like sucrose, lactose, maltodextrin and the like or water insoluble like microcrystalline cellulose, partially pregelatinized starch, dicalcium phosphate and the like. Biguanide and rate controlling polymer can be coated as single layer or as separate layers on to these inert cores; or granulated with the inert cores; or mixed with inert cores and extruded and spheronized to form the pellets.

The coating can be applied to the inert/active core using a conventional coating pan or a spray coater, or a rotating perforated pan or an automated system, a fluidized bed process or any other suitably automated coating equipment.

The extended-release core containing biguanide may optionally be coated to seal the core. The coated active cores may be dried under conditions effective for drying e.g. in an oven or in a fluidized bed dryer.

Finally beads/pellets comprising extended release and immediate release portions can be filled into capsules or compressed to form the tablets.

A randomized, two-treatment, two-period, two-sequence, single dose, crossover bioavailability study was performed using, tablets of the present invention and comparing with Actos 15 mg (containing pioglitazone hydrochloride) tablets (Takeda, USA) and Glucophage XR 500mg (containing Metformin hydrochloride) tablets (Bristol-Myers Squibb, USA) administered together in twelve healthy, adult, male, human subjects under fasting conditions. The tablets of the present invention were found to be bioequivalent to the reference products (Actos 15 mg tablets + Glucophage XR 500 mg tablets).

The present invention is further illustrated by the following examples. Those skilled in the art will find it apparent that various modifications and variations can be made to the formulations of this invention.

EXAMPLE 1

	INGREDIENTS	Mg/tablet
CORE	Metformin Hydrochloride	500
	Microcrystalline Cellulose	245
	Sodium Carboxymethyl Cellulose	150
	Purified Water	q.s.
	Hydroxypropyl methylcellulose	100
	Magnesium Stearate	5
SEAL COAT	Hydroxypropyl methylcellulose E5	15.6
	Polyethylene glycol 4000	4.8
	Titanium Dioxide	2.4
	Talc	1.2
	Purified Water	q.s.
ACTIVE COAT	Pioglitazone Hydrochloride equivalent to Pioglitazone (30 mg)	39.672
	Caprylocaporyl Macrogolglycerides	18
	Hydroxypropyl methylcellulose E5	40.3
	Polyethylene glycol 4000	12.4
	Titanium Dioxide	6.2
	Talc	3.1
	Purified Water	q.s.

Procedure:

1. Metformin hydrochloride was milled through 1 mm screen and mixed with microcrystalline cellulose and sodium carboxymethyl cellulose. The blend was sieved through No. 44 mesh, transferred to Rapid mixer granulator and wet granulated with purified water. The granules were dried in Fluid bed dryer, sized through multimill and sifted through No. 30 mesh.
2. Hydroxypropyl methylcellulose was separately sifted through No.30 mesh and mixed with granules in a low shear mixer. The blend was then mixed with magnesium stearate and compressed into tablets.

3. A coating dispersion was prepared by dispersing all ingredients of seal coat in water. The tablets were coated with this dispersion till weight build up of 2% w/w.
4. To prepare the active coat, caprylocaproyl monoglyceride was dissolved in purified water. To this solution, pioglitazone hydrochloride was added with stirring to form dispersion. The other ingredients of the active coat were added with stirring and the resulting dispersion was then coated upon the tablets obtained from step 3, using spray-coating, up to a weight build up of 10% w/w.

EXAMPLE 2

	INGREDIENTS	Mg/tablet
CORE	Metformin Hydrochloride	500
	Microcrystalline Cellulose	245
	Sodium Carboxymethyl Cellulose	150
	Hydroxypropyl methylcellulose	100
	Magnesium Stearate	5
SEAL COAT	Hydroxypropyl methylcellulose E5	15.6
	Polyethylene glycol 4000	4.8
	Titanium Dioxide	2.4
	Talc	1.2
	Purified Water	q.s.
ACTIVE COAT	Pioglitazone Hydrochloride equivalent to Pioglitazone (30 mg)	39.672
	Caprylocaporyl Macrogolglycerides	18
	Hydroxypropyl methylcellulose E5	40.3
	Polyethylene glycol 4000	12.4
	Titanium Dioxide	6.2
	Talc	3.1
	Purified Water	q.s.

Procedure:

1. Metformin hydrochloride was milled through 1 mm screen and mixed with microcrystalline cellulose and sodium carboxymethyl cellulose. The blend was sieved through No. 44 mesh.
2. Hydroxypropyl methylcellulose was separately sifted through No.30 mesh and mixed with the blend in a low shear mixer. The blend was then mixed with magnesium stearate and compressed into tablets.
3. A coating dispersion was prepared by dispersing all ingredients of seal coat in water. The tablets were coated with this dispersion till weight build up of 2% w/w.

4. To prepare the active coat, caprylocaproyl monoglyceride was dissolved in purified water. To this solution, pioglitazone hydrochloride was added with stirring to form dispersion. The other ingredients of the active coat were added with stirring and the resulting dispersion was then coated upon the tablets obtained from step 3, using spray-coating, up to a weight build up of 10% w/w.

EXAMPLE 3

	INGREDIENTS	Mg/tablet
CORE	Metformin Hydrochloride	500
	Microcrystalline Cellulose	245
	Sodium Carboxymethyl Cellulose	150
	Hydroxypropyl methylcellulose	100
	Magnesium Stearate	5
SEAL COAT	Hydroxypropyl methylcellulose E5	15.6
	Polyethylene glycol 4000	4.8
	Titanium Dioxide	2.4
	Talc	1.2
	Purified Water	q.s.
ACTIVE COAT	Pioglitazone Hydrochloride equivalent to Pioglitazone (15 mg)	19.836
	Caprylocaporyl Macrogolglycerides	14.4
	Hydroxypropyl methylcellulose E5	40.3
	Polyethylene glycol 4000	12.4
	Titanium Dioxide	6.2
	Talc	3.1
	Purified Water	q.s.

Procedure:

1. Metformin hydrochloride was milled through 1 mm screen and mixed with microcrystalline cellulose and sodium carboxymethyl cellulose. The blend was sieved through No. 44 mesh.
2. Hydroxypropyl methylcellulose was separately sifted through No.30 mesh and mixed with the blend of step 1 in a low shear mixer. The blend was then mixed with magnesium stearate and passed through roller compactor and then milled again to form granules. These granules are then compressed into tablets.
3. A coating dispersion was prepared by dispersing all ingredients of seal coat in water. The tablets were coated with this dispersion till weight build up of 2% w/w.
4. To prepare the active coat, caprylocaproyl monoglyceride was dissolved in purified water. To this solution, pioglitazone hydrochloride was added with stirring to form dispersion. The

other ingredients of the active coat were added with stirring and the resulting dispersion was then coated upon the tablets obtained from step 3, using spray-coating, up to a weight build up of 8.0% w/w.

A comparative in vitro dissolution profile of metformin hydrochloride in innovator's marketed tablets (Glucophage XR 500 mg) and tablets made in accordance with Example 3 was obtained. The dissolution was carried out in USP Apparatus Type I (basket) at a speed of 100 rpm. The medium was 900ml phosphate buffer, pH 6.8. The data obtained is disclosed in Table 1.

Table 1: Comparative in vitro dissolution profile of metformin hydrochloride in Glucophage XR 500 mg vs tablets made in accordance with Example 3.

Time (hrs)	**Percent release of metformin (%)**	
	Glucophage XR tablets	**Tablets of Example 3**
1	29	28
2	41	43
4	60	65
8	83	92
10	90	100
12	99	101

From the results, it is clearly evident that both the formulations have substantially similar dissolution profiles.

A comparative in vitro dissolution profile of pioglitazone hydrochloride in innovator's marketed tablets (Actos 15 mg) and tablets made in accordance with Example 3 was obtained. The dissolution was carried out in USP Apparatus Type I at a speed of 100 rpm. The medium was 900ml 0.1 N hydrochloric acid. The data obtained is disclosed in Table 2.

Table 2: Comparative in vitro dissolution profile of pioglitazone hydrochloride in Actos 15 mg tablets vs tablets made in accordance with Example 3.

Time (min.)	Percent release of pioglitazone (%)	
	Actos 15 mg tablets	**Tablets of Example 3**
15	100	95
30	101	104
45	101	106

From the results, it is clearly evident that more than 95% of the drug is released in 15 minutes and both formulations show substantially similar dissolution profiles.

Pharmacokinetics

The drug release was evaluated in vivo in a randomized, two treatment, two period, single dose, crossover bioavailability study. The study was conducted in 12 healthy, adult male human subjects under fasting conditions. A single tablet made in accordance with Example 3 (TEST) was administered after an overnight fasting of 10 hours with 240ml of 20% glucose water. These were compared with pioglitazone tablets 15 mg (Actos manufactured by Takeda Pharmaceuticals, USA) and metformin extended release 500mg tablets (Glucophage XR tablets manufactured by Bristol-Myers Squibb, USA) (REFERENCE). There was a washout period of seven days in between treatments. All subjects were on fast overnight for a period of 10 hours before commencement of dosing. Drinking water was not allowed from one - hour pre-dosing to 10 hour post dosing. Uniform and low fat meals were provided to all the subjects.

The plasma pioglitazone and metformin concentrations were measured by high performance liquid chromatographic (HPLC) method using ultraviolet (UV) detector.

Results: Pioglitazone : The formulation of present invention showed a Tmax of 2.9 ± 0.1287 hrs. as compared to 3.02 ± 0.3608 hrs. of reference formulation, indicating that test and reference formulations have nearly same mean values.

The formulation of present invention gave a serum concentration time profile similar to the reference formulation. The peak serum concentration (Cmax) was comparable to that for the reference formulation, indicating a similar rate of absorption of pioglitazone. The total bioavailability of pioglitazone measured as area under the curve (AUC 0- ∞) was also comparable to that of reference tablets, indicating that the entire drug was released from the formulation and absorbed during its transit through gastrointestinal tract. The results are presented in Table 3:

Table 3: Bioavailability parameters for test and reference formulations of pioglitazone

Parameters	**Reference**	**Test**
Cmax (ng/ml)	743.588 ± 67.44	727.724 ± 118.21
Tmax (hr)	3.02 ± 0.3608	2.90 ± 0.1287
AUC (0-∞) (ng/ml.hr)	5835.98 ± 1284.71	5554.94 ± 1232.29

Further, the extent of absorption for the test product was comparable to that for reference product as indicated by the ratio of test to reference (T/R ratio). The 90% confidence intervals were found to be within the bioequivalence acceptance range of 80-120% for the untransformed data as per Drugs Controller General of India draft guidelines The results are shown in Table 4.

Table 4: 90% Confidence intervals for untransformed data

Parameters	**Ratio (%) (Test/Reference)**	**90% Confidence Intervals**
Cmax (ng/ml)	97.75	90.97 - 104.53
AUC (0-∞) (ng/ml.hr)	94.79	86.92 - 102.66

Metformin: The formulation of the present invention showed a Tmax of 3.88 ± 0.8013 hrs. as compared to 3.58 ± 0.8940 hrs. of reference formulation, indicating that test and reference formulations have nearly same mean values.

The formulation of present invention gave a serum concentration time profile similar to the reference formulation. The peak serum concentration (Cmax) was comparable to that for the reference formulation, indicating a similar rate of absorption of metformin hydrochloride. The total bioavailability of metformin measured as area under the curve ($AUC_{0-\infty}$) was also comparable to that of reference tablets, indicating that the entire drug was released from the formulation and absorbed during its transit through gastrointestinal tract. The results are presented in Table 5.

Table 5: Bioavailability parameters for test and reference formulations of metformin.

Parameters	**Reference**	**Test**
Cmax (ng/ml)	633.227 ± 109.33	670.527 ± 116.392
Tmax (hr)	3.58 ± 0.8940	3.88 ± 0.8013
AUC (0-∞) (ng/ml.hr)	4653.866 ± 1463.9	4380.234 ± 1110.44

Further, the extent of absorption for the test product was comparable to that for reference product as indicated by the ratio of test to reference (T/R ratio). The 90% confidence intervals were found to be within the bioequivalence acceptance range of 80-120% for the untransformed data (as per DCG1 draft guidelines). The results are shown in Table 6.

Table 6: 90% Confidence intervals for untransformed data

Parameters	**Ratio (%) (Test/Reference)**	**90% Confidence Intervals**
Cmax (ng/ml)	107.24	96.23 - 118.25
AUC (0-∞) (ng/ml.hr)	96.43	84.07 - 108.79

WE CLAIM:

1. A process for preparing a pharmaceutical composition for oral administration comprising a combination of a biguanide and a glitazone wherein the biguanide is present as extended-release form and the glitazone is present as immediate release form in a single dosage form.

2. A process according to claim 1 wherein the said combination provides mean peak serum concentration and area under the curve comparable to that obtained for biguanide extended-release and glitazone conventional tablets given together.

3. The process according to claim 1 wherein the biguanide may be selected from metformin, phenformin, buformin and the like.

4. The process according to claim 3 wherein the biguanide is metformin.

5. The process according to claim 1 wherein the glitazone may be selected from troglitazone, pioglitazone, ciglitazone, rosiglitazone, englitazone and the like.

6. The process according to claim 5 wherein the glitazone is pioglitazone.

7. The process according to claim 1 wherein the biguanide is released into said environment of use over a period of 4 to 36 hours.

8. The process according to claim 7 wherein said period is 8 to 24 hours.

9. The process according to claim 1 wherein composition may be administered in the form of tablets or capsules.

10. The process according to claim 9 wherein tablet is a coated tablet.

11. The process according to claim 9 wherein tablet is a bilayered tablet.

12. The process according to claim 9 wherein capsules contains pellets, beads. granules, multiparticulates, tablets or powder.

13. The process according to claim 1 wherein the biguanide is incorporated in an extended-release core.

14. The process according to claim 13 wherein the core comprises a matrix.

15. The process according to claim 14 wherein the matrix comprises a uniform mixture of biguanide, and rate controlling polymers.

16. The process according to claim 15 wherein the rate controlling polymers may be hydrophilic, hydrophobic or a combination thereof.

17. The process according to claim 15 wherein the matrix may contain other pharmaceutical acceptable excipients in addition to the biguanide and rate controlling polymers.

18. The process according to claim 17 wherein the pharmaceutically acceptable excipients are selected from diluents, lubricants , binders, glidants, coloring and flavouring agents.

19. The process according to claim 1 wherein the biguanide is layered onto pharmaceutically inert core or seeds.

20. The process according to claim 19 wherein the biguanide layer is further surrounded by rate controlling polymer layer.

21. The process according to claim 19 wherein the inert seeds or core may be water soluble or water insoluble.

22. The process according to claim 1 wherein the glitazone is incorporated into an exterior coating.

23. The process according to claim 22 wherein the coating comprises water-soluble polymers.

24. The process according to claim 23 wherein the coating may contain other pharmaceutical acceptable excipients in addition to the glitazone and water soluble polymers.

25. The process according to claim 24 wherein the pharmaceutically acceptable excipients are selected from wetting agents, plasticizers, opacifiers and colorants.

26. The process according to claim 25 wherein the wetting agents may be selected from hydrophilic and hydrophobic surfactants.

27. The process according to claim 22 wherein the coating is applied to tablets.

28. The process according to claim 22 wherein the coating is applied to granules or beads.

29. The process according to claim 1 wherein the glitazone is present as pellets.

30. A process for preparing a pharmaceutical composition for oral administration comprising a combination of metformin and pioglitazone wherein metformin is present as extended-release form and pioglitazone is present as immediate release form in a single dosage form.

31. A process according to claim 30 wherein the said combination provides mean peak serum concentration and area under the curve comparable to that obtained for metformin extended-release and pioglitazone conventional tablets given together.

Dated this 14TH day of **November, 2002.**

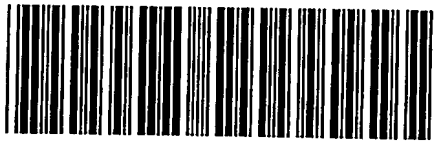
For Ranbaxy Laboratories Limited

Vinay Kumar Kaul

(Sushil Kumar Patawari)
Company Secretary

PCT Application

IB0305140



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